respectfully request reconsideration and withdrawal of all rejections.

Before beginning a discussion of the Office Action, Applicant would like to restate an objective of the present invention. As can be seen in the present specification, the present invention provides a solution to the problem of finding liposome complexes of polydeoxyribonucleotides that possess a high degree of stability (see line 5 of page 2 of the specification) and also a long-lasting efficacy (lines 21-22 of page 4). This problem, however, has not been addressed in the references cited in the Office Action.

Rejections of claims 1-12 and 19-22 under 35 U.S.C. § 103(a)

The Examiner has advanced that Claims 1-12 and 19-22 are obvious under 35 U.S.C. 103(a) in view of the Litzinger, Maccarone, and Eastmann references.

It is observed that the Examiner's stated in the Office Action (see lines 5-8, page 3, of the Office Action) that the Litzinger, Maccarone and Eastmann references teach that nucleic acids do not possess the ability to cross a cell membrane, but that they are able to do so once they are complexed with cationic liposomes. Thus, the Examiner has conceded that the nucleic acids of the cited references do not possess the required pharmacological activity of the present invention and that the nucleic acids of the references only become effective drugs with the claimed transfection ability when they are complexed with liposomes.

It is submitted that the depolymerized polydeoxyribonucleotides of the present invention are not similar to the nucleic acids disclosed in the above references and that

the claimed depolymerized polydeoxyribonucleotides are, therefore, not rendered obvious by the cited references.

It is submitted that it is known (see for instance, Gursoy et al. Pharmazie 48 (1993) pages 549-550, copy attached hereto) that the present oligonucleotides, which are different from the nucleic acids of Litzinger, Maccarone or Eastmann, are effective as drugs even when they are not combined with cationic liposomes. Therefore, it is submitted that the present invention is different from the inventions contained within the cited references as the oligonucleotides used in the present invention can be used without complexation with a liposome. This property is not found in the cited reference and is, in fact, taught away from. Therefore, it is submitted that the 103 rejection is improper because the cited references fail to teach the claimed invention. Thus, it is requested that the rejection be withdrawn for this reason.

The Gursoy reference describes an anti-inflammatory experiment according to the pharmacological model of rat paw edema (see paragraph 3, "Animal Experiment", on page 550). The results of the experiment are reported in Table 2 on page 550. The column on the right side of the table reports results obtained 6 hours after the administration of the drug to the subjects. From this column the following is noted:

1) that injection of the vehicle saline solution (sodium phosphate buffer - PBS), used to dissolve the tested compounds (group I), brought about an average increase of paw volume of 63.9 (control group);

2) that administration of depolymerized polydeoxyribonucleotides having mol. wt.

16,000 (see the 1st paragraph under the title on page 549) at a dose of 120 mg/Kg (group II) reduced the average increase of paw volume to 41.1.

This shows result illustrates that depolymerized polydeoxyribonucleotides, such as those of the present invention, are effective drugs even if they are administered without a cationic liposome; and

3) that an injection of a weight quantity of depolymerized polydeoxyribonucleotides complexed with liposomes, equal to 1/150 of that used in group (II), i.e., 800 µg instead of 120 mg used in (II) (see under paragraph 3 "Animal Experiments" on page 550 of Gursoy), reduced the average increase of the paw volume to 30. (See the results in the last right column of Table II for groups V and VI.)

These results show that in the experimental model of inflammation, complexation with liposomes affords to reduce the administered quantity of the polydeoxyribonucleotides, with improved anti-inflammatory effectiveness. However, it does not eliminate the fact that the oligonucleotides can be used without the complexed liposomes.

Therefore, in view of the fact that the depolymerized polydeoxyribonucleotides of the present invention do not require complexation with liposomes in order to be effective drugs and that the oligonucleotides of Litzinger, Eastmann and Maccarone acquire pharmacological activity only after complexation with liposomes, it is submitted that the teachings of the Litzinger, Eastmann and Maccarone references are not applicable to the pending claims.

Further, because the claimed invention utilizes oligonucleotides with different properties and characteristics than those disclosed in the cited references, it is submitted that the 103 rejection is improper. The cited references fail to teach the present invention. Therefore, it is requested that this rejection be withdrawn.

It is also submitted that the problem solved by the present invention was not that of providing a pharmacological activity to depolymerized polydeoxyribonucleotides (as shown by the Gursoy reference's demonstration of pharmaceutical activity prior to complexing with liposomes), but instead providing stable pharmaceutical formulations that comprise stable liposome complexes of the depolymerized polydeoxyribonucleotides. Such an invention, of course, is not shown in Gursoy, as Applicants have previously noted (see page 3, lines 5-14, of the specification). Therefore, it is respectfully submitted that the Examiner may have misunderstood the present invention and it is requested that reconsideration be given to the bases for the rejection contained in the Office Action.

Additionally, it is noted that on page 3 of the Office Action, 3rd full paragraph, the Examiner stated that while the classical definition of "transfection" is directed towards genetic material, this term is also used to describe the therapeutic molecules (besides nucleic acids) to a recipient.

In support of the above position, the Examiner cited the Lee patent (U.S. Patent No. 5,908,777), and, in particular, the abstract and column 3, lines 20-27.

It is noted that the abstract of the Lee patent discloses a method for creating a lipidic vector for delivering a therapeutic molecule. This method entails bringing the molecule into contact with a polycation to form a complex, and then mixing the complex with an anionic lipidic preparation. Peptides can also be added to the preparation. A stable lipidic vector of reduced immunogenicity and cytotoxicity and of enhanced transfection activity is then obtained. Therefore, unlike the present invention, the Lee patent discloses a pharmaceutically less effective composition.

From column 3, lines 20-27, it is observed that the lipidic vector of the Lee patent is intended for delivering nucleic acids (line 23 of column 3) and other molecules of therapeutic value, that (1) are less cytotoxic, (2) induce less immune response, (3) are less prone to aggregation, and hence, (4) deliver a higher concentration of DNA.

It is also noted that other molecules of therapeutic value may be found in column 5, lines 6-9. These molecules include hormones, growth factors, secondary metabolites and synthetic pharmaceutical compounds, and antigenic substances useful for raising immune response.

Column 4, lines 12-14, shows the principle and steps involved in the preparation of liposome encapsulating DNA vectors, called lipidic vectors. See also column 7, lines 23-46.

According to the Lee patent, the following compounds can be added to the lipidic vector:

1) Folate (as a targeting ligand) see line 17 of column 7.

The targeting ligand, as explained at lines 43-44 of column 5, will deliver the nucleic acid to the targeting cells.

2) Fusogenic peptide, see lines 23-24 of column 7.

Lines 35-37 of column 3 indicate that the fusogenic peptides enhance transfection of cells by means of the lipidic vector.

It is also noted that Example 2 (see column 9 of the Lee patent) describes an experiment wherein KB cells were transfected with DNA-containing folate-targeted liposomes (lines 20-21 of column 9).

The Lee patent noted the following regarding the experiment:

1) At low lipid to DNA ratio (<6) transfection of the KB cells was efficient and could not be inhibited by addition of 1mM folic acid (lines 23-25 of column 9).

2) At a lipid to DNA ratio of 6 transfection was higher than with the cationic liposome DNA/DC-chol complex (lines 28-31 of column 9).

3) At higher lipid to DNA ratios (>10) transfection appeared to be receptor-mediated, since it could partially be blocked by free folic acid (lines 32-35 of column 9).

Therefore, the experiment described in the Lee patent studied the transfection ability of DNA in the DNA-liposome complex lipidic vector of the U.S. patent.

It is noted that the term "transfection" in Lee is clearly referring to DNA-liposome complexes. The Applicant also notes that throughout the Lee patent "transfection" is

never used to describe the activity of complexes of liposomes with compounds different from DNA.

Therefore, it is submitted that the Examiner's statement that "transfection" is a term known to be used for transfer of therapeutic molecules besides nucleic acids to a recipient in view of Lee, is lacking in support because Lee clearly uses the term to refer to the activity of liposome-DNA complexes.

It is again submitted that the term "transfection activity", as previously argued by the Applicant, has a very specific pharmacological meaning. This term is directed towards the transfer of genetic information, as reported in the dictionaries. Attached for the Examiner's consideration is the definition given on page 1253 of "Webster's Ninth New Collegiate Dictionary" for "transfection." As can be seen, the definition of the term matches that advanced by the Applicant and not the Examiner.

Further, it is noted that the Lee patent reiterates that a technical problem of Lee is the instability of the liposome complexes with deoxyribonucleic acid (see column 1, lines 54-60). Lee describes a mechanism by which said liposome complexes in aqueous solution become unstable and concludes that for clinical application said complexes should be freshly prepared. Therefore, Lee, unlike the present application, does not supply an answer to the question posed by the present application. In fact, Lee teaches away from a stabilized complex in its teaching that the complexes should be freshly prepared.

Additionally, the Applicant examined the liposome complexes with

depolymerized nucleic acids described in prior publications and has observed that they, too, are relatively unstable.

In the examples of the present application, it is shown (see Tables I-III on pages 27-29) that the liposome complexes of depolymerized polydeoxyribonucleotides according to the prior art (such as Gursoy), over a period of 30 days, lose, on the average, about 74% of the pharmacological activity determined immediately after preparation of the pharmaceutical aqueous formulation.

The Applicant submits that the results obtained in the examples of the application are sufficient to overcome the Examiner's objection as they are representative of the formulations taught in the cited references.

Therefore, it is submitted that the comparative experimental data presented in the Specification confirm the statement in the Lee patent that the DNA liposomes recited in the cited publications are not stable. It is also submitted, then, that the Examiner's statement on lines 7-8 of page 4 of the Office Action that "Lee's statement is a general statement as background of his invention and Lee does not provide any experimental data" is irrelevant to the present invention. It is submitted that the Applicant has proven the validity of the previous statements regarding Lee and the stability of its compositions in the specification, this Response, and the previous filing.

In the paragraph bridging pages 3-4 of the Office Action, the Examiner stated that

"...whether claimed polydeoxyribonucleotides have the classical transfection

ability is not the issue. The issue is whether the cationic liposomes taught by the prior art are able to deliver, as vectors, the claimed art known polydeoxyribonucleotides to the intended donors, and the prior art clearly shows the ability of the cationic liposomes to perform this function...".

The Applicant remarks that the issue discussed in the above comment is not part of the present invention and submits that it is, therefore, irrelevant to the present discussion.

It is again submitted that the primary objective of the invention was not to provide a vector to deliver polydeoxyribonucleotides to the intended donor. Instead, the invention is directed to depolymerized polydeoxyribonucleotide-liposome complexes that are more stable than those already known, in order to achieve an improved stability of the corresponding pharmaceutical formulation.

An improved stability means that the pharmaceutical formulation has a longer shelf life. Therefore, it is submitted that the above Examiner's statement deals with an issue already met in the references and fails to address the subject matter of the present invention (an extended stability). Thus, it is requested that the rejection be withdrawn for this reason as well.

It is also noted that on page 4 of the Office Action, the Examiner stated that Litzinger, Maccarone and Eastmann do not teach or suggest any instability.

It is submitted that the experiments described in said references were made following an acute treatment scheme, i.e., the liposome complex was prepared and

thereafter used altogether in the pharmacological experiment. Therefore, there was no time or inclination to study the stability of the formulations in the cited references and the fact that the cited references do not discuss such cannot be construed by the Examiner as a statement that the formulations were, indeed, stable. In fact, the teachings of the Gursoy reference show the fallacy of this logic. It is requested that the Examiner note that the Applicant has demonstrated in the present application that DNA-liposome complex instability becomes evident after a period of several days or weeks.

Therefore, Litzinger, Maccarone and Eastmann were not in a position to detect any instability as they used the formulations immediately upon preparation. It is requested that the rejection be withdrawn for these reasons as well as the fact that the cited references do not discuss nor disclose heightened stability properties.

The Examiner also stated, addressing the Zelphati reference, that stability of polydeoxyribonucleotides in liposome complex is logical, since nuclease cannot digest them (lines 10-12 of page 4 of the Office Action).

In the Amendment filed on July 17, 2002, it was argued (lines 5-7 of page 6) that the Zelphati reference discloses a general property of complexes of cationic liposomes and oligonucleotides, once they are delivered to the cells. It was also stated on lines 12-15, page 6, of the Amendment that the problem of the present invention was not that of improving the pharmacokinetic profile of depolymerized polydeoxyribonucleotides.

It is requested that the Examiner note that the results of Table 2 of Gursoy confirm the Applicant's argument with respect to Zelphati. After administration of the

liposome complex to the animals (see the results given for groups V-VI that correspond to those treated with the polydeoxyribonucleotide-liposome complex) pharmacological activity reaches a maximum on the third hour and then remains fairly constant up to the end of the experiment (6th hour).

This result shows that the Zelphati arguement is correct, since once administered in vivo to the experimental animal, even at such a low administered dose of 1800 µg (see under paragraph 3 "Animal experiment" on page 550 of Gursoy) the polydeoxyribonucleotide concentration in the blood remains fairly constant, indicating that it is protected from endogenous endonuclease digestion. Therefore, the pharmaceutical efficacy of the compositions remained unchanged, supporting Applicants' previous arguments.

In view of the above, the Applicants submit that the Examiner's statement that "If the cationic liposome-oligonucleotide complexes are stable in this hostile environment, it is reasonable for one of ordinary skill in the art to expect the complexes to be stable in an aqueous buffer environment" is baseless because it has no experimental support, nor is there any prior publication, etc. provided that supports the Examiner's position.

The Applicant remarks again that efficacy of the pharmaceutical form is <u>not</u> the technical problem addressed by the present invention, nor is it of relevance for the solution presented in the present application. It is requested that the Examiner note the following paragraph bridging pages 4-5 of the Specification:

"...This affords to use the aqueous emulsions containing the complexes of the invention for subsequent treatment, for one or more days, and also for long lasting administrations, such as infusions."

This paragraph clearly shows that the "stability" meant by the Applicant is the stability, or shelf life, of the pharmaceutical formulation used for the administration of polydeoxyribonucleotide-liposome complexes and not that argued by the Examiner.

Therefore, the Applicant concludes that the stability to nuclease attack, i.e., the constant oligonucleotide blood levels disclosed by Zelphati, could not suggest to one skilled in the art that the complex could be shelf stable for periods of days or weeks, as found by the Applicant.

As stated previously, no references provided by the Examiner address the present invention. The Applicant has demonstrated that with the liposome complexes of depolymerized polydeoxyribonucleotides of the art it is not possible to prepare stable pharmaceutical formulations. In fact, all of the above-commented prior art do not even mention the problem solved by the present invention. Therefore, it is submitted that the rejection is improper for these reasons as well and it is requested that the rejection be withdrawn.

Finally, it is noted that the Examiner has not been able to cite any part of the above articles where the issue of shelf stability is mentioned and an indication is given to those skilled in the art to prepare liposome complexes of depolymerized polydeoxyribonucleotides having high stability in time.

The Examiner, to fill this gap in his arguments, has stated that stability is inherent to the combination of compounds as for the present claim 1. In making the above statement, the Examiner has used the knowledge of the present invention. This is an impermissible use of hindsight and renders the rejection improper for this reason as well. It is requested that the rejection be withdrawn on this ground.

It is submitted that the present application is patentable and Notice of Allowance be issued.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper referencing Attorney Docket No. 108907-09014.

Respectfully submitted,

D. Daniel Dzara, II
Registration No. 47,543

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W., Suite 400
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

DDD:ksm

Enclosures: Page 1253 of Webster's Ninth New Collegiate Dictionary
Gursoy Reference
Petition for Extension of Time (one month)